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Review Article

Pulmonary fibrosis: A short- or long-term sequelae of severe COVID-19?

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ABSTRACT

The pandemic of coronavirus disease 2019 (COVID-19), caused by a novel severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2), has caused an enormous impact on the global healthcare. SARS-CoV-2 infection primarily targets the respiratory system. Although most individuals testing positive for SARS-CoV-2 present mild or no upper respiratory tract symptoms, patients with severe COVID-19 can rapidly progress to acute respiratory distress syndrome (ARDS). ARDS-related pulmonary fibrosis is a recognized sequelae of COVID-19. Whether post-COVID-19 lung fibrosis is resolvable, persistent, or even becomes progressive as seen in human idiopathic pulmonary fibrosis (IPF) is currently not known and remains a matter of debate. With the emergence of effective vaccines and treatments against COVID-19, it is now important to build our understanding of the long-term sequela of SARS-CoV-2 infection, to identify COVID-19 survivors who are at risk of developing chronic pulmonary fibrosis, and to develop effective anti-fibrotic therapies. The current review aims to summarize the pathogenesis of COVID-19 in the respiratory system and highlights ARDS-related lung fibrosis in severe COVID-19 and the potential mechanisms. It envisions the long-term fibrotic lung complication in COVID-19 survivors, in particular in the aged population. The early identification of patients at risk of developing chronic lung fibrosis and the development of anti-fibrotic therapies are discussed.

Introduction

The coronavirus disease 2019 (COVID-19) is caused by a novel severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2). COVID-19 rapidly developed into a global pandemic, and the outbreak has caused enormous impacts on the global healthcare as well as economy. Although COVID-19 is a multi-organ disease, SARS-CoV-2 infection primarily targets the respiratory system.[1] The clinical spectrum associated with COVID-19 is diverse. Most people who tested positive for SARS-CoV-2 were asymptomatic or presented mild upper respiratory tract symptoms. However, patients with severe COVID-19 can rapidly progress to respiratory distress requiring intensive care treatment and mechanical ventilation (MV).[2] Patients who survive the acute phase of COVID-19 pneumonia are at risk of developing deleterious consequences on lung function, most notably pulmonary fibrosis.[3–6] Given the scale of the pandemic and the number of people requiring invasive ventilation, the burden of post-COVID-19 lung fibrosis is likely to rise in the next years. As effective vaccines and treatments become available, it is now important to build our understanding of the sequela of SARS-CoV-2 infection in the lungs and to identify the subpopulation of patients who are at high risk for the development of chronic pulmonary fibrosis.

This review aims to summarize the pathogenesis of COVID-19 in the respiratory tract. It highlights pulmonary fibrosis associated with acute respiratory distress syndrome (ARDS) post-SARS-CoV-2 infection and discusses the potential mechanisms underlying ARDS-related lung fibrosis. It envisions the long-term fibrotic lung complication in COVID-19 survivors, particularly in the aged population. It addresses an early identification of patients at risk of developing pulmonary fibrosis and the development of effective anti-fibrotic therapies.

The pathogenesis of COVID-19 in the lung

SARS-CoV-2 infection primarily targets the respiratory tract. SARS-CoV-2 encodes 27 proteins including 4 structural proteins (nucleocapsid, envelope, membrane, and spike proteins), 16 non-structural proteins (NSP1–NSP16) required for virus replication (RNA-directed RNA polymerase, helicase, and other components), and 7 uncharacterized accessory proteins (open reading frame [ORF] 3a–ORF8).[7] The spike glycoprotein protein is responsible for the binding of cellular receptors and subsequent cell entry. Effective SARS-CoV-2 infection requires host furin cleavage of the spike protein at its S1/S2 junction and S2 sites.[8] The fusion of viral and cellular membranes also involves enzymatic cleavages by transmembrane protease serine 2 (TMPRSS2) and other proteases

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such as cathepsins.[9] These findings indicate that SARS-CoV-2 tropism is dependent on the host expression of both viral cognate receptors and proteases.

Angiotensin-converting enzyme 2 (ACE2) is the main receptor for both SARS-CoV and SARS-CoV-2.[10] High-sensitivity RNA *in situ* mapping analysis revealed that the ciliated nasal epithelial cells have the highest level of ACE2 expression with decreasing expression throughout the lower respiratory tract.[11] In parallel with the pattern of ACE2 expression, SARS-CoV-2 infectivity is high in the nasal epithelium followed by a marked reduction down to the bronchial and alveolar epithelia.[11] Once inside the cell, viral RNAs and proteins interact with host RNAs and proteins to produce new infectious virions.[12,13] The infectivity of patients with SARS-CoV-2 peaks before the onset of symptoms.[14] As a result, presymptomatic transmission became a key driver of the pandemic.

A summary report of 72,314 COVID-19 cases from the Chinese Center for Disease Control and Prevention indicated that around 80% of individuals infected with COVID-19 were asymptomatic or presented only mild symptoms, mostly restricted to the upper and conducting airways.[15] These individuals can recover completely without specific treatments. Approximately 20% of patients deteriorated, often within 7–10 days after the onset of symptoms. In severe COVID-19 cases, about 25% of individuals developed severe pneumonia manifested by bilateral lower-zone pneumonias and diffuse alveolar damage (DAD) which might progress to ARDS, especially the aged individuals or individuals with co-morbidities, such as hypertension, diabetes, and obesity.[16] Patients with severe COVID-19 accounted for almost all of the SARS-CoV-2-associated comorbidities and mortalities.[17]

Molecular and cellular mechanisms related to COVID-19 pathophysiology remain unclear. Studies have shown that both an inappropriate pro-inflammatory host immune response and a diminished antiviral interferon (IFN) response were associated with severe COVID-19.[18,19] The viral particles released from cells can induce the release of proinflammatory cytokines, causing widespread alveolar epithelial damage.[20] In the majority of patients with SARS-CoV-2 infection, SARS-CoV-2-infected alveolar macrophages produced chemoattractants for T cells. T cells then produced IFN-γ to further induce the release of inflammatory cytokines from alveolar macrophages and further promote T cell activation.[21] The findings suggest that SARS-CoV-2-containing alveolar macrophages and IFN-γ-secreting T cells establish a positive feedback loop that drives persistent alveolar inflammation in patients with severe COVID-19. Because of a dysregulated immune response and a reduced ability to repair the damaged epithelium, aged individuals are particularly at risk for developing severe COVID-19. Additionally, a reduced mucociliary clearance in the elderly may render the virus more readily to spread to the alveoli. The lung pathology in severe COVID-19 is characterized by progressive loss of epithelial–endothelial integrity, septal capillary injury, complement deposition, intravascular viral antigen deposition, and localized intravascular coagulation.[22] It has been found that SARS-CoV-2 RNA interacts with both the RNA and protein components of the host mitochondria, resulting in the changes of mitochondrial shape and size.[13] Together, these findings suggest a functional link between SARS-CoV-2 and host mitochondria, which might inform future studies to understand the mechanisms of viral pathogenesis.

COVID-19 ARDS-related lung fibrosis

ARDS is the most frequent complication of severe COVID-19 disease and is highly prevalent among fatal cases. 7.2–31.0% of individuals hospitalized for COVID-19 suffer from SARS-CoV-2-induced ARDS.[17] Pulmonary fibrosis is a recognized sequelae of ARDS.[23,24] The presence of fibrotic changes in the acute phase of COVID-19 can be identified on tomographic scans, including architectural distortion, ground-glass and reticular opacities, and honeycombing, associated with functional impairment. The most common chest computed tomography (CT) manifestations of severe COVID-19 were bilateral ground glass opacities (GGOs) with or without consolidation, and with the preference for lower lobes.[25–27] CT findings demonstrated significant increases in fibrous shadows, manifested by fibrous stripes, subpleural lines, and traction bronchiectasis, in multiple lung lobes at the early recovery stage, indicating pulmonary fibrosis.[28] A systematic review of the chest CT findings in 4410 adult patients with COVID-19 showed that patients who suffered severe or critically severe pneumonias had more extensive involvement in consolidations.[20] The peak of the CT lesions was reached at around 10–11 days of the onset of symptoms before gradually resolving or persisting as patchy fibrosis for up to 4 weeks. This study also showed that the consolidations as well as multilobar involvement were more frequently observed in the older individuals, whereas GGOs appeared more common in younger adults, suggesting that CT manifestations in patients with COVID-19 vary by age and disease severity. Analyses of patients recovered from severe COVID-19 revealed that a substantial proportion of patients experienced residual impairment of lung function, such as impaired gas transfer and reduced total lung capacity, consistent with pulmonary fibrosis.[29] Pulmonary fibrosis in fatal cases of COVID-19 is characterized by fibroblast proliferation and airspace obliteration, in which micro-honeycombing was predominantly present at the autopsy.[30] Extensive lung fibrosis has also been observed in explanted lungs from COVID-19 patients who received lung transplants for the end-stage ARDS.[31] Systematic analysis of gene expression profiles in COVID-19 autopsy samples provided further evidence for COVID-19 ARDS-related lung fibrosis. It has been shown that fibrosis-related pathways were among the major up-regulated transcriptional signatures in lung tissue obtained from patients who died of COVID-19.[32,33] Proteomic analysis demonstrated elevated expression of fibrosis markers, including serpine 1, chitinase 3-like 1 (CHI3L1), lysosomal cathepsins (cathepsin L1 and cathepsin D), and interleukin-17 receptor A (IL17RA) in 144 autopsy lung samples from 19 COVID-19 patients.[4]

Potential mechanisms underlying SARS-CoV-2-induced lung fibrosis

The molecular basis responsible for the profibrotic response to SARS-CoV-2 infection is not fully understood yet. Previous studies suggest that direct viral effects, altered gene expression profile, dysregulation of host immune response, local thromboembolism and hypercoagulability due to altered vascular permeability, and mechanical ventilation-induced lung injury (VILI) may contribute to SARS-CoV-2-induced lung fibrosis.[34,35] [Fig. 1].

ACE2, the major cellular receptor of SARS-CoV-2, is an important component of the renin–angiotensin system (RAS). ACE2 converts angiotensin II (Ang II) to heptapeptide Ang-(1−7), a functional antagonist of Ang II. Ang II has fibrogenic effects through upregulating expression of the profibrotic cytokine transforming growth factor (TGF)-β1, whereas Ang-(1−7) lowers cytokine secretion, reduces inflammation, and protects the lung from injury and fibrotic remodeling.[36] Previous studies have shown that ACE2 is downregulated in animal models of pulmonary fibrosis as well as human idiopathic pulmonary fibrosis (IPF).[37] SARS-CoV infection downregulates ACE2 expression and reduces ACE2 activity.[38,39] Consistent with these findings, it has been reported that serum levels of Ang II were elevated in COVID-19 patients compared with the healthy individuals, and were correlated with the viral load and lung injury.[40] Taken together, the downregulation of ACE2 upon SARS-CoV-2 infection may disturb the activities of RAS, resulting in increased inflammation and lung fibrosis.

The spike protein of SARS-CoV-2 contains an arginine (Arg)-glycine (Gly)-aspartic acid (Asp) (RGD) integrin-binding domain.[41], which mediates the binding of SARS-CoV-2 to integrins, including TGF-β-activating $\alpha v\beta 3$ and $\alpha v\beta 6$ integrins.[41,42] Previous studies have found that the nucleocapsid protein of SARS-CoV directly enhances TGF-β signaling.[43] Whether SARS-CoV-2 can activate TGF-β by an integrin-dependent mechanism similar to SARS-CoV remains to be determined. Additionally, the binding of SARS-CoV-2 with ACE2 has been shown

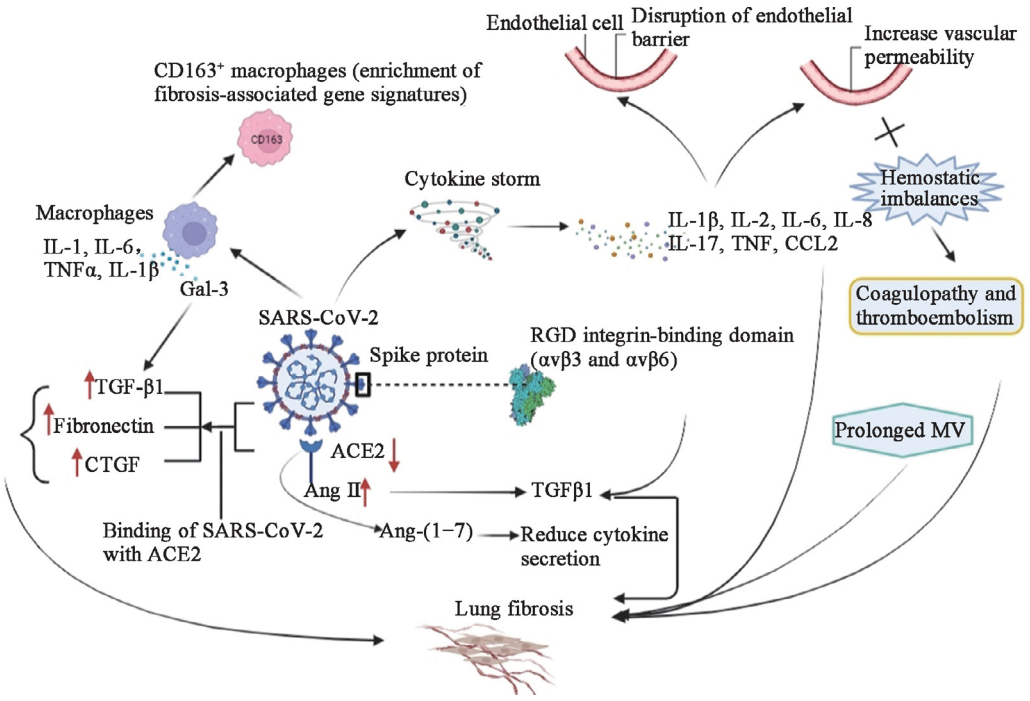

Fig. 1. Potential mechanisms underlying pulmonary fibrosis associated with COVID-19. Diagram was created via Biorender.com. ACE2: Angiotensin-converting enzyme 2; Ang II: Angiotensin II; Ang-(1–7): Angiotensin 1–7; CCL2: Monocyte chemoattractant protein-1; COVID-19: Coronavirus disease 2019; CTGF: Connective tissue growth factor; Gal-3: Galectin-3; IL: Interleukin; MV: Mechanical ventilation; RGD: Arginine (Arg)-glycine (Gly)-aspartic acid (Asp); SARS-CoV-2: Severe acute respiratory syndrome (SARS) coronavirus 2; TGF-β1: Transforming growth factor -β1; TNF: Tumor necrosis factor.

to increase messenger RNA (mRNA) levels of TGF-β1, connective tissue growth factor (CTGF), and fibronectin.[44], suggesting that SARS-CoV-2 infection may drive lung fibrosis by activating fibrosis-related genes.

The cytokine profiling analyses showed that COVID-19 patients with severe ARDS had increased levels of interleukin (IL)-1β, IL-2, IL-6, IL-17, IL-8, tumor necrosis factor (TNF), and monocyte chemoattractant protein-1 (MCP-1/CCL2) manifesting the macrophage-associated syndrome (MAS, also known as the “cytokine storm”).[45] IL-1β and TNF-α accumulated rapidly in response to SARS-CoV-2 infection followed by a sustained expression of IL-6.[46] Inflammatory cytokines including IL-6 have a profound effect on the pro-fibrotic activities of fibroblasts.[47] Although lung fibrosis normally develops gradually, the cytokine storm associated with severe COVID-19 can thicken and scar the small airways extensively within just a few days.[48] It is currently unknown why certain individuals are able to recover from SARS-CoV-2-induced lung injury, whereas others continue developing epithelial dysfunction and aberrant repair leading to fibrosis.

Recently, a subset of CD163-expressing monocyte-derived macrophages was found to drive a profound fibroproliferative tissue response in severe COVID-19.[49] CD163$^+$ macrophages were characterized by an enrichment of fibrosis-associated gene signatures reminiscent of macrophage populations found in IPF.[49] This study suggests the role of pro-fibrotic macrophages in the development of fibroproliferative COVID-19 ARDS. Additionally, SARS-CoV-2 infection increased the secretion of galectin-3 (Gal-3), an important mediator of pulmonary fibrosis, by macrophages. Macrophage-derived Gal-3 upregulated expression of TGF-β receptors on fibroblasts and myofibroblasts through a paracrine fashion, leading to fibrous tissue formation.[50] Furthermore, Gal-3 contributed to the release of proinflammatory cytokines such as IL-1, IL-6, TNFα, and IL-1β.[51] Together, these findings highlight the critical role of macrophage-derived Gal-3 in post-COVID-19 pulmonary fibrosis.

Severe COVID-19 is characterized by lung endothelial cell dysfunction.[52] Proinflammatory cytokines, such as IL-1β and TNF-α, can activate glucuronidases that degrade the glycocalyx of endothelial cells, affect intercellular junctions, and enhance cell contractility. These result in the disruption of endothelial barrier function and increased vascular permeability.[53] Altered vascular permeability and hemostatic imbalance can lead to coagulopathy and thromboembolism, which are implicated in the pathogenesis of lung fibrosis.[54] Analysis of cardiopulmonary histopathology of COVID-19 showed the presence of thrombotic/thromboembolic vascular occlusions in the majority of patients.[55] Together, the dysfunction of endothelial cells plays a critical role in the initiation of post-infection pulmonary fibrosis and vascular remodeling.

Mechanical ventilation is the most important supportive therapy for COVID-19-related ARDS. It is well known that the initial inflammatory injury of ARDS to the lung can be augmented by the mechanical forces of MV.[56] Prolonged MV is a potential contributing factor to the development of ARDS-related pulmonary fibrosis.[57]

Lung fibrosis in the aftermath of COVID-19: reversible, persistent, or progressive?

The majority of patients with COVID-19 pneumonia survive the acute phase. While post-COVID-19 pulmonary fibrosis can be diagnosed based on clinical, radiologic, and pathologic findings, the appropriate timing for a diagnosis of irreversible pulmonary fibrosis has not been established yet.[58] It is currently unclear whether survivors of severe COVID-19 could develop long-term lung complications and whether COVID-19-related pulmonary fibrosis would eventually resolve, persist long-term or become progressive as observed in human IPF.[3]

One study found that chest CT scores of pulmonary fibrosis in most COVID-19 patients were significantly improved 30 days, 60 days, and 90 days after discharge,[59] suggesting that post-COVID-19 lung fibrosis is likely to regress over time. This study also found that pulmonary fibrosis in some patients did not completely resolve within 90 days. Similarly, a separate study found that most COVID-19 patients demonstrated resolution of lung fibrosis by week 5, but those with more se-

vere pneumonia had persistent GGOs.[60] Whether the residual fibrotic lesions observed in these studies would completely disappear requires further observation. Studies also suggest that younger patients are more likely to have complete resolution of the CT manifestations,[61] and patients with <50% and predominantly peripheral involvement are more likely to have a better disease outcome and a lesser chronic involvement.[62]

Although it is too early to determine whether the COVID-19-associated fibrotic changes in the lung are irreversible, recent investigations of the prevalence of radiological and functional consequences post-COVID-19 demonstrated that lung fibrosis can persist in some patients across different follow-up times. In one study, CT scans found parenchymal bands with a pattern of fibrous residual changes in almost all mechanically ventilated survivors of COVID-19 at a 3-month follow-up after discharge, in which half of the patients were accompanied by other signs of fibrosis, including parenchymal distortion, volume loss, and/or bronchiolectasis.[63] Another study found that the fibrous bands on chest CT remained unchanged in one-fifth of patients after 3 months.[64] Imaging manifestations of interstitial changes and pulmonary fibrosis have also been found up to 6 months after the onset of COVID-19 symptoms in patients with severe COVID-19 pneumonia.[65] An Italian study involving a total of 220 COVID-19 cases reported that 20% of the patients presented persistent lung abnormalities at 6 months after hospitalization for COVID-19 pneumonia.[66] Another Chinese study found fibrotic-like changes in the lung in more than one-third of 114 patients who survived severe COVID-19 pneumonia.[65] Furthermore, the fibrotic changes in the lung were associated with an older age, ARDS, longer hospital stays, tachycardia, non-invasive MV, and higher initial chest CT score.[65] In a prospective study of 84 participants with moderate COVID-19 pneumonia, fibrotic-like abnormalities, including pleuro-parenchymal bands, linear atelectasis, and bronchiectasis/bronchiolectasis, became appreciable in 50% of the participants at 3 months. The fibrotic changes and baseline chest CT GGOs were still presented in 2% of the participants at 1 year,.[67] suggesting that post-COVID-19 pulmonary fibrosis can persist at least 1 year after SARS-CoV-2 infection in a subpopulation of patients.

While there are insufficient data to predict the natural course of pulmonary fibrosis in COVID-19, the long-term sequelae of SARS-CoV-2 infection can be extrapolated from previous coronavirus outbreaks, namely the severe acute respiratory syndrome coronavirus (SARS-CoV; known as SARS) outbreak and the Middle East respiratory syndrome coronavirus (MERS-CoV; known as MERS) outbreak. Long-term studies with SARS and MERS have shown the fibrotic lung changes in recovered patients. A 15-year follow-up study of 71 patients with SARS showed that chronic pulmonary fibrosis existed in 38% of patients after the original infection, in which 4.6% of patients were accompanied by reduced forced vital capacity (FVC), indicative of impaired lung function.[68] Although the follow-up investigation of patients recovered from MERS is limited in the literature, there is radiographic evidence of pulmonary fibrosis in about a third of patients at a median of 43 (range 32–320) days after hospital discharge.[69] Given nearly 30% of SARS and MERS survivors show persistent radiological and physiological abnormalities consistent with fibrotic lung disease, it is conceivable that lung fibrosis may be a possible long-term complication of COVID-19 patients. Long-term follow-up studies will be required to establish the true prevalence of post-COVID-19 fibrosis.

IPF is a progressive fibrotic lung disease in which lung function inexorably declines, leading to respiratory failure and eventually death. Although COVID-19-related pulmonary fibrosis and IPF differ significantly with regard to their clinical, radiological, and histopathologic features.[70], it has been found that lung sections from patients with early phase COVID-19 pneumonia presented characteristic fibroblastic foci similar to usual interstitial pneumonia (UIP)/IPF.[71] Transcriptomic analyses revealed that COVID-19 lung disease shared cytopathic macrophages and alveolar type II cell features with IPF.[49,72,73] It remains to be seen whether COVID-19 itself causes progressive pulmonary fibrosis.

Identification of COVID-19 patients at risk of developing chronic lung fibrosis and potential anti-fibrotic therapies

The early identification of the subpopulation of patients at risk of developing persistent/progressive lung fibrosis is of great importance. Many factors may potentially impact whether post-COVID-19 lung fibrosis can stabilize for a long period of time or even become progressive. Increased age is known as a major risk factor for human IPF. Cellular changes occurring with aging, such as cellular senescence, stem cell exhaustion, and extracellular matrix (ECM) deregulation, might reduce the ability of lung cells to respond effectively to SARS-CoV-2, triggering pathways that promote dysregulated repair and persistent fibrosis. Senescence results in a cellular state known as the senescence-associated secretory phenotype (SASP). The senescence-associated increase in cytokines, matrix remodeling proteases, and growth factors is particularly detrimental for cells in the lung, which requires tight regulation of ECM remodeling and inflammatory responses to prevent abnormal tissue repair.[74] It has been established that senescent cells contribute to the pathogenesis of IPF.[75]

Stem cells from patients with IPF showed impaired regenerative capacity.[76] Stem cell exhaustion and reduced ability to properly differentiate during lung tissue repair may represent the fundamental cause of age-related lung diseases, including IPF. Studies aiming at the construction of a single-cell atlas of COVID-19 lung showed a reduction in type II alveolar epithelial progenitor (AT2) cells and the presence of keratin 8 $(KRT8)^{+}$ pre-alveolar type 1 transitional cell state (PATS) and $TP63^{+}$ intrapulmonary basal-like progenitor cells (IPBLP). These results suggest that multiple regenerative strategies are invoked to re-establish alveolar epithelial cells lost to SARS-CoV-2 infection.[77] It is known that the failure of epithelial progenitors to regenerate at a sufficient rate can promote lung fibrosis.[78,79]

Aging tissues are characterized by an increase in the formation of advanced glycation end-products (AGEs).[80] The ECM, in particular collagen matrix, is highly sensitive to glycation due to a slow turnover rate.[81] AGEs drive non-enzymatic crosslinking of the ECM, thereby contributing to matrix stiffening.[82] In a recent study, we demonstrated that AGE crosslinking is increased in aged lungs and occurs at an accelerated rate in lung fibrosis; increased AGE crosslinking contributes to lung matrix stiffening.[83] Since mechanical interactions between contractile myofibroblasts and the stiffened ECM can provide a feedforward mechanism that sustains and/or perpetuates pulmonary fibrosis,[84] matrix stiffening in aged lungs could be a contributing factor that promotes the fibrotic complication in COVID-19 patients.

Genome-wide association studies (GWAS) have identified common genetic variants that confer the risk of IPF.[85] It has been reported that there is a positive genome-wide genetic correlation between IPF and severe COVID-19 risk.[86] This raises the possibility that COVID-19 patients with genetic alterations associated with IPF might be at risk of developing persistent or progressive post-COVID-19 fibrosis. Follow-up genome-wide studies on COVID-19 patients will shed light on the role of genetics in driving post-COVID-19 fibrosis. Fibrocytes have been shown to present in the bronchioalveolar lavage (BAL) fluids and expand in the bone marrow, blood, and lung of both patients with ARDS and animal models of lung injury, correlating with poor outcomes.[87,88] The findings support the idea that fibrocytes might represent a useful biomarker for the stratification of COVID-19 for developing chronic lung fibrosis.

Corticosteroids can prevent the development of acute lung injury and ARDS by reducing the host inflammatory response in viral pneumonia. There is evidence that corticosteroids mitigated the short- and long-term effects of COVID-induced pneumonia and improved the symptoms of post-COVID pulmonary fibrosis by decreasing lung inflammation.[89] However, the beneficial effects of corticosteroids are often offset by their serious side effects, including obesity, immune depression, depressive disorders, and osteoporosis, mainly when used at high doses and over a long period of time.[90] Further clinical trials are needed to address the utility and risks of corticosteroid in post-COVID-19 pulmonary fibrosis.

Table 1
Potential therapeutic options for post-COVID-19 lung fibrosis.

Therapeutics	Mechanism of action	Reference
Corticosteroids	Anti-inflammatory activity	89
Pirfenidone/deupirfenidone (LYT-100)	Suppression of NLRP3 inflammasome activation, inhibition of multiple profibrotic signal pathways, downregulation of IL-6 expression, and inhibition of collagen secretion and collagen fibril formation	89,92–95
Nintedanib	Downregulation of the profibrotic gene expression, inhibition of collagen secretion and collagen fibril formation	95
$\alpha v\beta 6$ integrin inhibitor	Blockade of $\alpha v\beta 6$ integrin-dependent latent TGF-β activation	97,98
Azithromycin	Prevention of SARS-CoV-2–host interactions, anti-inflammatory activity, protection of lung epithelial integrity	99
MSCs	Anti-inflammatory, immunosuppressive, antifibrotic, and angiogenic properties; promotion of lung repair and regeneration	101,102

COVID-19: Coronavirus disease 2019; IL-6: Interleukin 6; MSCs: Mesenchymal stem cells; NLRP3: Nucleotide binding oligomerization domain (NOD)-like receptor thermal protein domain associated protein 3; SARS-CoV-2: Severe acute respiratory syndrome (SARS) coronavirus 2; TGF-β: Transforming growth factor-β.

Antifibrotic drugs, pirfenidone and nintedanib, are effective in attenuating the rate of lung function decline in patients with IPF. These drugs might be beneficial for inhibiting profibrotic pathways in SARS-CoV-2 infection. Pirfenidone exerts anti-fibrotic, anti-inflammatory, and anti-oxidative properties.[91] It ameliorates lipopolysaccharide-induced acute lung injury and subsequent fibrosis by suppressing nucleotide binding oligomerization domain (NOD)-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome activation.[92] Pirfenidone has been shown to reduce the levels of IL-6, a key mediator of the "cytokine storm" after SARS-CoV-2 infection, in both serum and the lung.[93] Additionally, pirfenidone suppresses furin, a protein effector involved in both the entry of SARS-CoV-2 and activation of TGF-β1, and modulates signaling pathways that are involved in the pathogenesis of post-COVID-19 pulmonary fibrosis, including Wnt/β-catenin and Yes-associated protein (YAP)/Hippo signaling pathways.[94] Deupirfenidone (LYT-100) is a selectively deuterated form of pirfenidone designed to attenuate the rate of drug metabolism, resulting in a differentiated pharmacokinetic profile that retains the pharmacologic benefits of pirfenidone while potentially improving tolerability. A clinical trial (NCT04652518) was initiated to evaluate its efficacy against post-acute COVID-19 respiratory diseases.[89] Both pirfenidone and nintedanib downregulate the profibrotic gene expression, reduce collagen secretion, and inhibit collagen I fibril formation.[95] Nintedanib may potentially increase the risk of bleeding in anticoagulated patients,[96] which may limit its usage in COVID-19 patients with coagulopathy and/or anticoagulant therapy. Drugs in development that target $\alpha v\beta 6$ might be also beneficial for the treatment of both severe COVID-19 and post-COVID-19 lung fibrosis.[97,98] $\alpha v\beta 6$ integrin is an endogenous activator of latent TGF-β whose activation is a major target for antifibrotic therapies. SARS-CoV-2 can potentially bind $\alpha v\beta 6$ and $\alpha v\beta 3$ integrins through an RGD integrin-binding domain close to the ACE2-binding region of the spike protein. Azithromycin can downregulate cytokine production, maintain epithelial cell integrity, and prevent SARS-CoV-2 binding and entry into pulmonary interstitial cells,[99] suggesting that this drug may prevent COVID-induced lung fibrosis through its immunomodulatory and antiviral properties.

Treatment with mesenchymal stem cells (MSCs) is considered a potential therapy for pulmonary fibrosis.[100] The anti-fibrotic effects of MSCs are related to their anti-inflammatory, immunosuppressive, and angiogenic properties. Small-scale studies on the efficacy of MSCs treatment in COVID-19 have demonstrated the remarkable reversal of symptoms in critically severe conditions.[101] While current anti-fibrotic drugs can only slow the fibrotic progression without reversing lung fibrosis, MSCs have the potential for regenerative capacity and reinstatement of healthy lung tissue structure and function. The MSC secretome contains both soluble proteins (cytokine, chemokine, and growth factors) and nano/microstructured extracellular vesicles (EVs), which may mediate the fibrotic lung regeneration through anti-inflammatory and antifibrotic properties.[102] An array of therapeutic options that are being studied and/or tested in clinical trials for the treatment of post-COVID lung fibrosis are summarized in Table 1.

Conclusions and future perspective

There is mounting evidence that severe COVID-19 patients develop ARDS-related fibrotic sequelae and the impairment of lung function indicative of restrictive lung disease. However, very little is known about the long-term consequence of this devastating pandemic. It remains a debate as to whether early fibrosis in survivors of COVID-19 will fully recover or progress into sustained fibrotic lung diseases.[103] Historically, patients who died of ARDS show evidence of pulmonary fibrosis, whereas ARDS survivors have relatively little fibrosis. Survivors of SARS followed up for 15 years exhibit low levels of pulmonary fibrosis with relatively normal lung function after rehabilitation.[68] Given the predilection of SARS-CoV-2 towards populations with demographic risk factors (e.g., aged population and male) and comorbidities similar to those of IPF, the burden of development of long-term fibrotic consequences may be significant. Due to the substantial number of people affected, even a small incidence of pulmonary fibrosis will have a significant impact. There are currently no long-term studies and no treatment guidelines to mitigate lung fibrosis associated with COVID-19. It is imperative to design studies for the identification of patients at high risk for the development of long-term fibrosis and whether fibrosis will affect lung function. Lastly, many of the current and emerging anti-fibrotic drugs could have therapeutic benefits for treating SARS-CoV-2 infection and preventing the long-term fibrotic consequences of severe COVID-19.

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Conflicts of interest

None.

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